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Protocol: _____

SSO₂ THERAPY POST-APPROVAL STUDY

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PROTOCOL SIGNATURE PAGE

SSO₂ THERAPY POST-APPROVAL STUDY

A MULTI-CENTER, NON-RANDOMIZED POST-APPROVAL STUDY OF SUPERSATURATED OXYGEN THERAPY (SSO₂) FOR 90 MINUTES IN ACUTE ANTERIOR MYOCARDIAL INFARCTION PATIENTS WITH SUCCESSFUL PCI/STENTING PRESENTING WITHIN ≤ SIX HOURS FROM TIME OF SYMPTOM ONSET UNTIL TIME OF REPERFUSION

I have read this protocol and agree to adhere to the requirements. I will provide copies of this protocol and all pertinent information to the study personnel under my supervision. I will discuss this material with them and ensure they are fully informed regarding the investigational devices and conduct of the study according to 21 CFR parts 50, 54, 56 and 812, to GCP as described in ICH guideline E6 and to hospital IRB/ethics committee requirements.

Clinical Site _____

Investigator Signature _____

Date _____

Investigator (PRINT) _____

PROTOCOL SUMMARY

Trial Name and Number: SSO₂ Therapy Post-Approval Study

Device:

SSO₂ Therapy requires the use of three primary components. These include a hardware device called the TherOx[®] DownStream AO System (AO System), a single-use disposable device called the TherOx[®] AO Cartridge (AO Cartridge) and the MI-Cath Infusion Catheter. The cartridge is loaded into and operated by the AO System; the cartridge has a tubing set that connects to an arterial sheath on the patient blood draw side and the infusion catheter on the blood/SSO₂ solution patient return side.

Study Objectives:

- Evaluate clinical outcomes in a cohort of real world patients receiving SSO₂ Therapy during commercial use by interventional cardiologists.
- Evaluate major complications, patient outcomes with adjunctive pharmacologic use.
- Evaluate clinical device and procedural success during commercial use.

Study Design:

This prospective, open label, multi-center, single arm study is designed to evaluate SSO₂ Therapy continued safety during commercial use in real world settings in patients following successful PCI/stenting within 6 hours after experiencing acute anterior myocardial infarction. Results will be compared to the clinical outcomes in a similar AMI patient population from the HORIZONS study.

Patient Enrollment:

404 patients consecutively enrolled at 20 – 40 sites in the United States of America.

Patient Follow-Up

Clinical follow-up will occur at 30, 180 days and at 1 year. Investigator or designee may conduct follow-up as telephone contact or office visit.

Primary Endpoint:

- Composite incidence rate of Major Adverse Cardiac Events (MACE) defined as death, myocardial infarction

(MI) and target vessel revascularization at 1 year. Non-inferiority test at a two-tailed 5% significance level with an assumed base rates of 10.7% based on the HORIZONS study data in each arm (SSO₂ Therapy and HORIZONS study data as control and a 6% proposed safety delta)

Secondary Endpoint:

- Death (any cause) assessed at 1 year (and evaluated by an exact 95% exact confidence interval with a desired upper bound of less than 6.5%).

Additional Safety Data

- Individual MACE component event rates assessed at 30 days, 180 days, and at 1 year.
- Stent occlusion assessed at 30 days, 180 days, and at one year.
- Bleeding events classified as serious through 30 days (or date of discharge from index procedure)
- Clinical, device, and technical success

All adverse event and procedural success evaluations to be performed by an independent Clinical Events Committee

**Patient Population
(Analytical Population):**

Anterior STEMI patients treated with PCI and stenting within 6 hours from time of symptom onset who receive adjunctive SSO₂ Therapy.

Safety Monitoring

An independent clinical events committee (CEC) will review and adjudicate according to pre-specified definitions for each of the clinical data elements, including: death, MI, stroke, target vessel revascularization, and SAE bleeding.

Study Blinding

This study is not blinded.

Treatment Strategy

It is recommended that each enrolling investigator review the DownStream AO System Instructions For Use and assess the contraindications, warnings and precautions sections with respect to risks and benefits for treating potential patients.

Key Inclusion Criteria: The patient agrees to participate in this study by signing the Institutional Review Board-Approved Informed Consent form. Qualifying patients will have AMI with successful PCI and stenting \leq six hours after time of symptom onset.

Key Exclusion Criteria: Inability to obtain Informed Consent. Cardiogenic shock and intra-aortic balloon pump (IABP) patients. Patients with significant co-morbidities that may compromise the primary endpoint evaluation at one year.

**Procedural
Requirements**

- Arterial Blood Gas sampling at baseline, 30, 60 and 90 minute intervals.
- Adequate anticoagulation therapy maintained throughout SSO₂ Therapy administration.
- See attached **Table 1** for required medical procedures and timeframes.

Study Sponsor:

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MEDICAL PROCEDURES AND TIMEFRAMES

Table 1 summarizes the required schedule for patient testing and data acquisition.

Table 1. Medical Procedures and Timeframes

	Informed Consent	Baseline Assessment	Blood Pressure	Arterial Blood Gas (ABG)	Heart rate/rhythm	ACT	Telephone or Office Visit Follow Up
Informed Consent	♥	♥		♥			
Post Index PCI/Stent procedure							
Baseline pO ₂ assessment							
30 min. SSO ₂ Infusion							
60 min. SSO ₂ Infusion							
At or after 30 days							♥
180 days ± 14 days							♥
1 Year ± 30 days							♥

1 INTRODUCTION

The DownStream AO System and disposable DownStream AO Cartridge and MI-Cath Infusion Catheter were approved for the delivery of SuperSaturated oxygen (SSO₂) Therapy for qualifying patients under an FDA approval order for PMA P080005 issued on [date]. SSO₂ Therapy was approved for use in patients experiencing anterior acute myocardial infarction revascularized by means of PCI with stenting within six hours of symptom onset. This approval was based in part on the results of the AMIHOT II clinical trial, which demonstrated a significant infarct size reduction in qualifying patients with no significant safety risk at 30 days, as compared to a Control group receiving PCI with stenting alone. This SSO₂ Therapy Post-Approval Study (SSO₂ PAS) will evaluate the clinical outcomes of patients who receive the therapy in a commercial setting, administered by a broader group of practicing interventional cardiologists at a variety of U.S. health care facilities. This protocol will evaluate patients over a

one-year time interval from the date of the procedure, and compare the clinical outcomes of these patients to a population of anterior AMI subjects receiving PCI within six hours of symptom onset from the HORIZONS trial database. This protocol will include all consecutively enrolled patients in the United States of America (USA) who consent to participate and receive SSO₂ Therapy, and agree to the terms of study follow and necessary procedures described herein.

2 BACKGROUND INFORMATION

2.1 SSO₂ History

The safety and effectiveness of SSO₂ Therapy was evaluated in two consecutive clinical trials, the AMIHOT I and AMIHOT II studies. After the promising AMIHOT I subset of anterior < 6 hr patients was identified, the goal of the AMIHOT II trial was designed to validate these results in a meaningful way. The AMIHOT II study was designed as a superiority study with respect to infarct size reduction, with no significant increase in 30-day Major Cardiac Adverse Event (MACE) rates in subjects receiving adjunctive SSO₂ Therapy. The study endpoints were met, and SSO₂ Therapy is the first PCI-adjunctive procedure to demonstrate an infarct size reduction, as measured by 14-day Tc-99 sestamibi SPECT imaging.

2.2 SSO₂ Approval

In the United States, TherOx SSO₂ Therapy administered with the DownStream AO System, DownStream AO Cartridge, and MI-Cath infusion catheter was approved for commercial use on [date]. Conformité Européene (CE) Mark approval for SSO₂ Therapy was received on 14 September 2001 allowing it to be marketed throughout the European Union.

2.3 SSO₂ Therapy

2.4 Description of the TherOx DownStream AO Devices

SSO₂ Therapy requires the use of three primary components. These include a hardware device called the TherOx[®] DownStream AO System, a single-use disposable device called the TherOx[®] AO Cartridge and an infusion catheter called the TherOx[®] MI-Cath Infusion Catheter. The AO Cartridge is loaded into and operated by the DownStream AO System; the cartridge has a tubing set that connects to an arterial sheath on the patient blood draw side and the infusion catheter on the blood/SSO₂ solution patient return side.

2.4.1 DownStream AO Cartridge

The AO Cartridge, shown in **Figure 1**, is an injection-molded polycarbonate device that creates SuperSaturated Oxygen (SSO₂) solution from inputs of hospital-supplied oxygen gas and saline solution, mixes the SSO₂ solution with the patient's own arterial blood, and delivers oxygen-enriched hyperoxemic blood to the infusion catheter for infusion into the coronary arteries. The methods used in creating the hyperoxemic blood are explained through examination of the three chambers of the AO Cartridge also shown below in **Figure 1**.

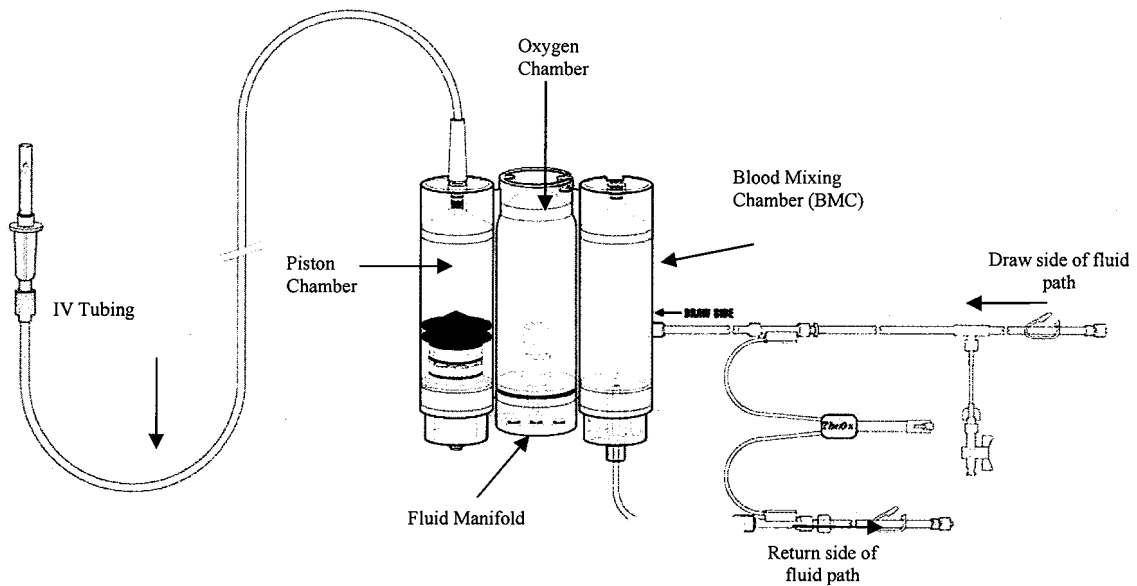


Figure 1. AO Cartridge

Saline is drawn into the Piston Chamber of the AO Cartridge from an intravenous (IV) bag. The Piston Chamber is, in effect, a motor-driven syringe pump that withdraws saline from the IV bag on the downstroke and pushes saline into the central Oxygen Chamber on the upstroke. The saline is pumped through a small nozzle that atomizes the liquid into discrete droplets for efficient oxygen uptake.

Oxygen gas is provided at a pressure of 600 psig, or approximately forty atmospheres, to the central Oxygen Chamber. Oxygen is dissolved into the atomized saline droplets to create hyperbaric SuperSaturated Oxygen, or "SSO₂"

solution, with a dissolved oxygen concentration approaching 1.0 ml O₂ (STP)/ml saline. A reservoir of SSO₂ solution is maintained at the bottom of the Oxygen Chamber.

SSO₂ solution flows continuously from the Oxygen Chamber at a rate of 3 ml/min through a capillary tube into the Blood Mixing Chamber, where it mixes with arterial blood that has been withdrawn from the patient. After combining SSO₂ solution with normoxemic arterial blood, the resultant oxygen-enriched hyperoxemic blood is returned through an infusion catheter at a total flow rate of 75 ml/min to the patient's coronary arteries. The pO₂ level of the super oxygenated-infused blood is maintained between 760 – 1000 mmHg.

The AO Cartridge utilizes medical grade polyvinyl chloride (PVC) tubing for blood withdrawal and return to the patient. The cartridge housing is constructed primarily of injection-molded medical grade polycarbonate, a common plastic material used in medical devices. The tubing and Blood Mixing Chamber (BMC) comprise the blood-wetted fluid path of the AO Cartridge.

The production and flow of SSO₂ solution are continuous within the AO Cartridge; control of these processes is maintained through the use of the Fluid Manifold shown in **Figure 1**. The Fluid Manifold connects and controls the flow of saline and SSO₂ solution between the three chambers of the cartridge with three needle valves and one check valve. The Piston Chamber delivers saline to the Fluid Manifold through a small tube. The saline can be delivered to the Oxygen Chamber through the atomizer to create SSO₂ solution, through a dilution port to adjust concentration, or directly to the (BMC) to flush the capillary tube. The SSO₂ solution's dissolved oxygen concentration is controlled by the AO System.

The AO Cartridge is equipped with a pressure transducer that monitors both the draw side and return side pressures in the device during operation; the transducer connects to the AO System. An IV spike and flexible tube are attached to the Piston Chamber, enabling easy connection to an IV bag during the procedure. The draw and return tubing are equipped with luer connections. The AO Cartridge is a single-use Ethylene Oxide (EtO)-sterilized device.

The draw tubing is connected to the patient with a luer fitting that is attached to the femoral access sheath. The return tube is attached to the infusion catheter that has been placed at the desired location within the coronary arteries. These connections are addressed in detail below.

2.4.2 Patient Connections

The AO Cartridge draw tubing connects to the same femoral arterial sheath that is used for angioplasty and stenting procedures. Sheath placement may be coaxial (in one femoral artery) or contralateral (in both the right and left femoral arteries), based on the physician's discretion.

The preferred coaxial configuration is shown in **Figure 2** and illustrates how arterial blood is withdrawn from the sidearm. A luer fitting connects the sidearm to the AO Cartridge drawtube.

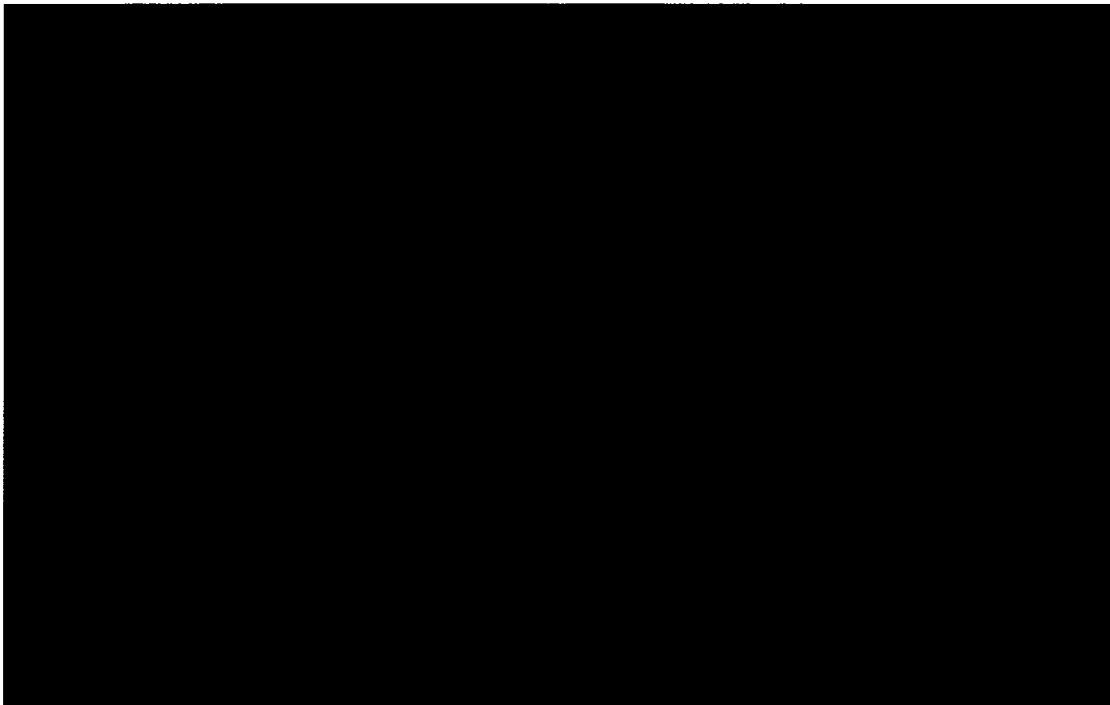


Figure 2. Co-Axial Draw/Return Clinical Configuration for SSO₂ Therapy

Note: **Figure 2** depicts an unprimed circuit for illustration purposes only.

The infusion catheter is placed through the guide catheter over a guidewire, to the target location within a coronary artery. The guidewire is removed prior to initiation of treatment. When extracorporeal blood flow is initiated, the infusion catheter and AO Cartridge return tube are wet-connected to ensure that no gaseous emboli are introduced to the patient during priming. Super oxygenated blood is infused through the infusion catheter shown in **Figure 2**. **Figure 3** provides a schematic of the patient connections during SSO₂ Therapy administration.

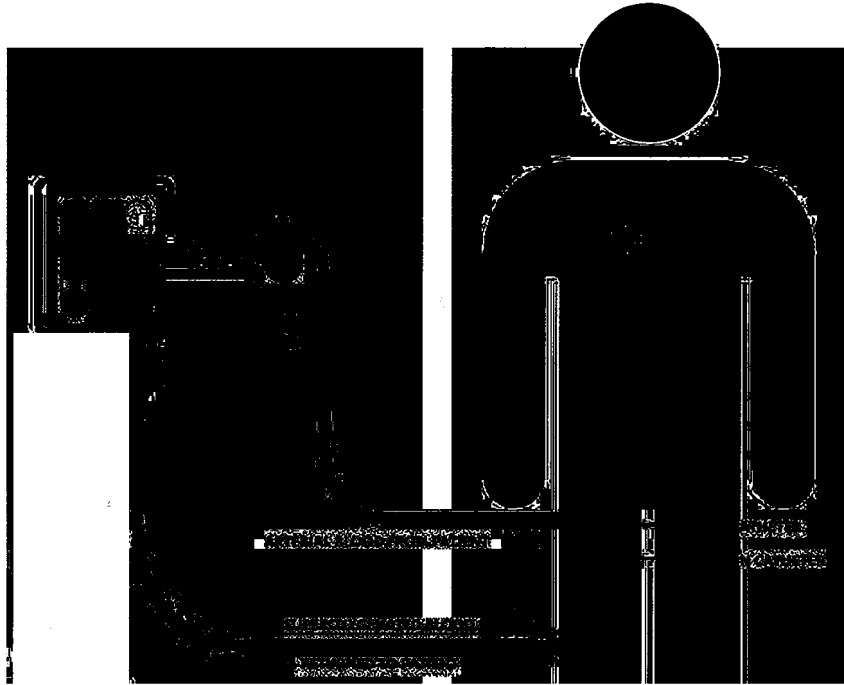


Figure 3. Schematic Representation of SSO₂ Therapy

2.4.3 DownStream AO System

The AO System (**Figure 4**) is the reusable hardware component that controls and monitors performance and safety during administration of SSO₂ Therapy. The mobile system stands approximately 5 feet tall with a footprint comparable to many devices that are currently used in a cath lab setting. The system can be operated in the cardiac catheterization laboratory (CCL), coronary care unit (CCU), or any other suitable location after the coronary infusion catheter is placed with the aid of fluoroscopy. The rear of the system has a built-in compartment that holds an E-bottle of medical-grade oxygen. An IV bag is suspended from a pole attached to the system. The hospital supplies the oxygen gas and sterile saline that are required to make SSO₂ solution. The AO System integrates several subsystems mounted on a single system chassis. These subsystems are described below.

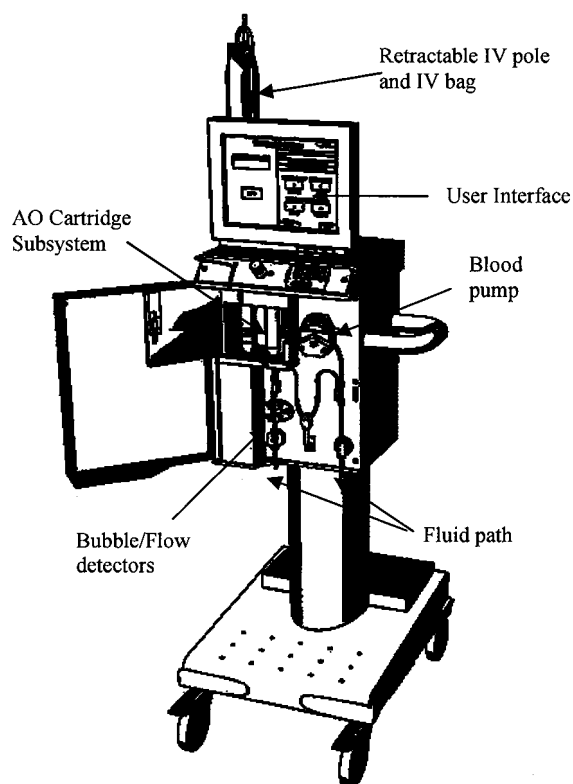


Figure 4. DownStream AO System

- The system chassis consists of a main enclosure mounted upon a system base, with four locking wheels. A retractable IV pole is mounted on top of the main enclosure.
- The AO Cartridge Subsystem (AOCS) is mounted inside the main enclosure. The AOCS houses and operates the DownStream AO Cartridge (the AOCS does not contact saline or blood). The AOCS provides the oxygen connection for the cartridge, and operates the valves that control the Fluid Manifold. A motor-driven piston ram engages the cartridge piston for operation of the Piston Chamber.
- The blood pump subsystem incorporates a peristaltic pump to withdraw normoxemic arterial blood from the patient's femoral artery, pump the blood through the Blood Mixing Chamber of the cartridge, and return super oxygenated blood via infusion catheter to the coronary arteries. The blood pump subsystem is equipped with a flow probe and feedback control that maintains a constant reperfusion rate of 75 ml/min during the administration of SSO₂ Therapy.

- The bubble detector is an ultrasound-based device that detects and measures the size of individual bubbles that pass through the extracorporeal circuit. The bubble detector will initiate a shutdown of the system if a gas volume of 10 microliters or greater is accumulated during SSO₂ Therapy administration.
- The Safety Interlock is an independent hardware circuit that shuts down treatment by stopping blood flow. The Safety Interlock continuously monitors system inputs for events that require treatment stoppage. The Safety Interlock contains no software and, in addition to its automatic shutdown capability, has a manually operated emergency stop button to disable SSO₂ Therapy regardless of any other input status.
- The User Interface is a touch-screen display that allows the user to initiate, monitor, and end the SSO₂ Therapy procedure.
- The AO System is equipped with an electronic power supply that provides DC power from AC input or from batteries that are self-contained within the system base.
- A hospital-supplied oxygen E-bottle with a yoke-type fitting is connected to the AO System pressure regulator to provide the oxygen supply. The pressure regulator controls oxygen gas charging to the cartridge.

3 STUDY OBJECTIVES

Study objectives consist of the following:

- Evaluate clinical outcomes in a cohort of real world patients receiving SSO₂ Therapy during commercial use by interventional cardiologists
- Evaluate major complications, patient outcomes with adjunctive pharmacologic use.
- Evaluate clinical device and procedural success during commercial use.

4 STUDY DESIGN

4.1 Study Design

The SSO₂ PAS is a prospective, multi-center, observational, single-arm registry/study to monitor SSO₂ Therapy continued safety during commercial use in real world settings. Results will be compared to the clinical outcomes in a similar AMI patient population from the HORIZONS study.

4.2 Patient Enrollment

404 patients will be enrolled consecutively in this study at 20-40 sites across the United States of America. Data from all study sites will be pooled for analysis.

4.3 Patient Follow-Up

Clinical follow-up will occur at 30, 180 days and at 1 year. The investigator or designee may conduct follow-up as telephone contacts or office visits.

4.4 Early Study Termination

No statistical rule for early trial termination is defined. However, TherOx, Inc. may discontinue the study at any stage with written notice to the investigator. Possible reasons for early termination may include the identification of safety risks that pose an unreasonable risk to the patient.

The Executive Committee makes a final decision for early study termination.

If a trial is terminated early, TherOx Inc. will provide a written statement describing why premature termination will occur, and notify the Institutional Review Board (IRB) and FDA. All applicable clinical study documents will be subject to the same retention policy as detailed in **Section 12** Data Handling and Record Keeping.

4.5 Measures Taken To Avoid / Minimize Bias

In order to minimize bias in assessing clinical events, an independent Clinical Events committee (CEC) (**Section 8.4.1** Clinical Events Committee) will be established.

4.6 Treatment Strategy

The treatment strategy will be determined by the investigator. It is recommended that each enrolling investigator review the most recent IFU to assess contraindications, warnings, and precautions for treating potential patients.

5 ENDPOINTS

5.1 Primary Endpoint

Composite incidence rate of Major Adverse Cardiac Events (MACE) defined as death, myocardial infarction (MI) and target vessel revascularization at 1 year. Non-inferiority test at a two-tailed 5% significance level with assumed base rates

of 10.7% based on the HORIZONS study data in each arm (SSO₂ Therapy and HORIZONS study data as control and a 6% proposed safety delta).

5.2 Secondary Endpoint

Death (any cause) assessed at 1 year (and evaluated by an exact 95% exact confidence interval with a desired upper bound of less than 6.5%).

5.3 Additional Safety Data

- Individual MACE component event rates assessed at 30 days, 180 days and at 1 year
- Stent occlusion events assessed at 30, 180 days and at 1 year
- Bleeding events classified as serious through 30 days (or date of discharge from index procedure)
- Clinical, device, and technical success

All adverse event and procedural success evaluations to be performed by an independent Clinical Events Committee.

6 PATIENT SELECTION AND WITHDRAWAL

6.1 Patient Population

Qualifying anterior STEMI patients treated with PCI /Stenting within 6 hours of symptoms onset who receive SSO₂ Therapy as an adjunct to their index procedure.

6.2 Patient Screening

All qualifying anterior STEMI patients admitted for PCI /stenting should be invited to participate in the study. All anterior < 6 STEMI patients will be entered into a Case Report Form (CRF) screening log. The screening log should list reasons for qualifying enrollment and fall-out.

6.3 Eligibility Criteria

6.3.1 General Inclusion Criteria

Candidates for this study must meet **ALL** of the following criteria:

1. Patient must be ≥ 18 years of age

2. AMI must be anterior
3. Complete medical history, history of AMI, previous coronary interventions, list of medications given within last 24 hours
4. 12-lead qualifying ECG criteria: Anterior infarction (ST-segment elevation ≥ 1 mm in two or more contiguous leads between V1 and V4 or new left bundle branch block (LBBB) with documentation of LAD system culprit lesion)
5. Patient provides written, Informed Consent
6. Patient and his/her physician agree to all required follow-up procedures and visits
7. Women of childbearing potential who have a negative pregnancy test (applies to female patients only)

6.3.2 General Exclusion Criteria

8. Patients with ventricular pseudoaneurysm, VSD, or papillary muscle rupture
9. Absolute contraindications to anticoagulant therapy, including hemorrhagic diathesis or thrombocytopenia
10. Systemic Arterial pO₂ is < 80 mmHg with supplemental oxygen
11. Placement of an intra-aortic balloon pump (IABP)
12. Patient has had coronary bypass surgery during the 30 day period preceding PCI
13. Severe known cardiac valvular stenosis or insufficiency, pericardial disease, or non-ischemic cardiomyopathy
14. Patients requiring cardiopulmonary resuscitation for > 10 minutes
15. Cardiogenic shock (SBP < 80 mm Hg for more than 30 minutes unresponsive to fluids or requiring intravenous pressors or placement of an IABP)
16. Expected survival of less than 12 months due to non-cardiac condition
17. Current participation in investigational device or drug trials that have not finished the primary efficacy endpoint follow-up parameters
18. Patient has had a hemorrhagic stroke during the 6-month period preceding PCI
19. Physician discretion regarding unacceptability for enrollment

6.3.3 Angiographic Inclusion Criteria

These are evaluated after the subject has provided signed Informed Consent but prior to randomization:

20. Based on coronary anatomy, PCI is indicated for culprit lesion with anticipated use of an Intra-Coronary Stent
21. TIMI 0, I, II or III flow is present on the initial angiographic injection of the infarct-related artery
22. Successful angioplasty as documented by < 50% diameter residual angiographic stenosis within and associated with the culprit lesion and \geq TIMI II flow and no major complications such as perforation or shock
23. Documented time of reperfusion is \leq 6 hours from the documented time of symptom onset

6.3.4 Angiographic Exclusion Criteria

24. Any proximal coronary diameter stenosis > 40 % that would restrict native flow with the infusion catheter in place
25. Infarct-related vessels that are either saphenous vein grafts and/or small second order coronary vessels that do not supply significant areas of myocardium
26. Presence of a non-stented coronary dissection upon completion of the PCI procedure
27. Unprotected left main diameter stenosis > 60%
28. Severe target vessel calcification or tortuosity
29. Multi – vessel disease that in the judgment of the investigator is best treated with emergent or urgent CABG or additional PCI within 30 days
30. In the investigator's opinion, the target vessel is unsuitable for either placing the infusion catheter or treatment with PCI

6.4 Patient Enrollment

The point of enrollment occurs when a patient or patient's legally authorized representative has provided written informed consent and only TherOx SSO₂ Therapy is initiated immediately post index PCI / Stent procedure. The study will sequentially enroll all consenting patients who have met these criteria.

6.5 Patient Discontinuation

Once enrolled, each patient should remain in the study until the required follow-up period is complete. However, the patient has the right to withdraw from the study at any time without penalty or loss of benefit. Data obtained to the last follow-up will be used for the analysis. The following events will result in terminating the patient's follow-up:

- Patient death
- Patient voluntary withdrawal
- Patient withdrawn by investigator as clinically indicated
- Patient lost to follow-up (unofficial withdrawal)
- Study is terminated according to section 4.4 Early Study Termination

Appropriate case report forms must be completed for both study-terminated patients and patients who complete the entire one-year follow-up. TherOx, Inc. must be notified of the reason for patient discontinuation. The site will provide this information on the appropriate case report form. Investigators must also report this information to the local IRB as defined by their institution's procedure.

6.5.1 Lost To Follow-Up

Patients that do not complete the scheduled follow-up visits and have not officially withdrawn from the study are considered lost to follow-up; this term does not apply to missed visits. Site personnel should make considerable effort to locate and communicate with the patient using all available methods (*e.g.*, telephone, emails, and postcards). The following contact procedure is recommended at each time point:

- A minimum of 2 telephone calls on different days over the specified follow-up windows should be recorded in the source documentation including date, time, and site personnel initials for staff attempting to contact the patient.
- If these attempts are unsuccessful, a certified letter should be sent to the patient.
- If the patient misses two (2) consecutive scheduled contact time points and the above mentioned attempts at communicating with the patient are unsuccessful, the patient will be considered lost to follow-up.

7 TREATMENT OF PATIENTS

The schedule of events for this trial is located in **Section 17.4** Schedule of Events.

The treatment strategy will be determined by the investigator. It is recommended that each enrolling investigator review the most recently updated IFU and assess the contraindications, warnings, and precaution sections for treating potential patients.

7.1 Anticoagulation / Antiplatelet Medication

SSO₂ Therapy involves the use of an extracorporeal circuit and therefore must be used in conjunction with an anticoagulation regimen of IV heparin to maintain Activated Clotting Times at 250 s or higher, or the equivalent per physician practice. Additional anticoagulation (antithrombotic) management is determined by each investigator. Enrolled patients will be encouraged to receive adjunctive dual antiplatelet therapy consisting of an indefinite duration of aspirin, along with clopidogrel per ACC/AHA guidelines.

7.2 Baseline

The baseline time point consists of clinical visits that occur up to four hours prior to the index procedure. Patients will be prepared according to the healthcare facility's standard care for interventional cardiology patients.

If available, the following data should be collected at baseline:

- significant medical history
- time from symptom onset to presentation
- HR, BP, Killip class
- thrombolytic treatment
- adherence to study inclusion/exclusion criteria, and baseline laboratory values
- PCI procedure variables including door to balloon time, presence of multi-vessel disease, lesion characteristics, pre- and post PCI TIMI flow, % stenosis, presence of dissection, stent type, and time to reperfusion, previous CABG and PCI, renal insufficiency, and anemia
- Other risk factors including tobacco use, family history of coronary artery disease, and stroke, hyperlipidemia
- Chronic concomitant medication
- Baseline Angiogram

Any of the above data that is not collected during the baseline time window may be obtained post-procedure and will still be considered baseline data; refer to **Section 17.4** Schedule of Events for specific time periods.

If available, the following pre-procedural laboratory assessments should be collected:

- Pre-procedural creatine kinase (CK), creatine kinase myocardial band isoenzyme (CK-MB), and/or troponin (the most recent assessment)

- Electrocardiogram (ECG)

7.3 Procedure

Following successful PCI/stenting, with all angiographic eligibility criteria and none of the exclusion criteria post stent deployment met, informed consent must be obtained and the patient may then be enrolled.

Anticoagulation must be maintained at protocol-specified levels throughout the duration of the SSO₂ Therapy procedure.

7.3.1 SSO₂ Therapy

7.3.1.1 Guiding Catheter and Arterial Sheath Selection

The coaxial (single arterial stick) approach is recommended for SSO₂ Therapy but not required. When only one arterial site (coaxial access) is used with the AO System, the size difference between the arterial sheath and the guide catheter must be 2 F (*e.g.*, an 8 F sheath with a 6 F guide catheter. With contralateral access, a 5.0 F or 6.0 F introducer sheath in an alternate arterial site (*i.e.*, radial, brachial, or contralateral femoral puncture) may be used. Ipsilateral insertion of a second sheath into the same femoral artery is strictly contraindicated.

The TherOx MI-Cath Infusion Catheter requires a minimum 6 F guiding catheter and 8 F arterial sheath for coaxial setup. If contralateral access is preferred, a minimum 5.0 F sheath is required to withdraw blood from the second arterial access site. **Table 2** provides a reference guide for contralateral or coaxial arterial access.

Table 2. Coaxial/Contralateral Arterial Access

	COAXIAL ACCESS	CONTRALATERAL ACCESS	
Access Site	Femoral Artery*	Femoral Artery**	Second Arterial Site***
Sheath	8 French	6 French	5 – 6 French
Guide Catheter	6 French	6 French	

***Coaxial access:** One femoral artery is used for both PCI/stenting and for withdrawing normoxic arterial blood and returning hyperoxemic blood. This configuration is recommended for SSO₂ Therapy.

****Contralateral access:** The femoral artery is used for PCI/stenting and for returning hyperoxemic blood from the DownStream System (“return” blood).

*****Contralateral access:** A second arterial access site is used for withdrawing blood for delivery to the DownStream System (“draw” blood).

Note: Ipsilateral insertion of a second sheath in a single femoral artery for SSO₂ Therapy is strictly contraindicated.

7.3.1.2 SSO₂ Infusion

The AO System will be inspected and prepared and SSO₂ Therapy will be initiated according to the IFU. There must be a 2 F size difference between the arterial sheath and the guide catheter (*e.g.*, 8 F sheath, 6 F guide catheter w/ TherOx MI-Cath Infusion Catheter) when only one arterial site (coaxial access) is used with the DownStream System. (Reference **Table 1**).

(Note: Refer to DownStream AO System Operators Manual for proper setup and operation)

1. For setup with the TherOx MI-Cath Infusion Catheter: if utilizing a single 8 F femoral arterial sheath for coaxial access, a guide catheter no larger than 6 F must be used.
2. For contralateral setup, the investigator has the option of inserting a smaller sheath (min. 5 F) in a second arterial access site for blood draw. The alternate access site may be a radial, brachial, or contralateral femoral artery to be determined by the investigator as appropriate for the patient. In this configuration, the sheath used to place the guide catheter may be smaller (*e.g.* 7 F sheath for 7 F guide catheter).
3. The guiding catheter is placed at the ostium of the infarct-related artery. After positioning of the guiding catheter, the infusion catheter is advanced over the guidewire into the infarct-related artery. Positioning of the infusion catheter within the infarct-related artery is at the discretion of the investigator for optimum infusion, but should not be placed distal to the stent.

4. Prior to initiation of SSO₂ Therapy, the investigator must remove the guidewire and recheck position of the infusion catheter under fluoroscopy. SSO₂ Therapy must be initiated in the cardiac catheterization laboratory. The investigator has the option of keeping the patient in the cath lab for the duration of the infusion or may transfer the patient to an appropriate holding area or the Critical Care Unit (CCU). All sheaths are required to be securely attached to the patient and checked for integrity prior to transport. The sheaths should be secured in the usual manner appropriate to CCL procedures for transport. The infusion catheter connection should be confirmed and placement checked prior to leaving the CCL if an alternate room for delivery of SSO₂ Therapy is used.
5. The AO System and AO Cartridge are set up per TherOx Instructions for Use, **Appendix VI**. The draw tubing of the AO Cartridge is connected to the sidearm of the draw sheath, and the return tubing of the AO Cartridge is connected to the proximal end of the infusion catheter.
6. The blood flow rate of the AO Cartridge is 75 ml/min and is controlled by the AO System.
7. Prior to initiation of SSO₂ Therapy, baseline systemic arterial pO₂ and blood pressure are recorded. The patient's systemic arterial pO₂ must be greater than or equal to 80 mmHg to proceed with SSO₂ Therapy. The DownStream System pO₂ range is set manually by the user after the baseline systemic arterial pO₂ is available.
8. When the AO System indicates readiness, infusion of SSO₂ solution may now be initiated. The time of initiation of SSO₂ infusion must be noted on the SSO₂ Therapy case report form.
9. SSO₂ Therapy infusion runs for 90 minutes. During this time the patient parameters such as blood pressure, systemic arterial pO₂, and heart rate/rhythm will be obtained at 30 minute intervals and recorded on the appropriate case report form. The pO₂ range on the AO System is updated as required based on changes in the patient's systemic arterial pO₂ reading.
10. The AO System automatically discontinues SSO₂ Therapy infusion after 90 minutes of SSO₂ Therapy. Normoxic blood continues to circulate through the circuit until the user manually shuts down the system, 5-10 minutes after SSO₂ infusion has stopped. The time of cessation of SSO₂ infusion must be noted on the SSO₂ Therapy Procedure case report form. The infusion catheter is withdrawn into the guiding catheter. The AO Cartridge tubing is clamped and disconnected from the sidearm of the arterial sheath and the infusion catheter. The catheters may be removed per normal catheterization procedures.

7.3.1.3 Device Performance

DownStream System and AO Cartridge device performance information, including date and time of SSO₂ Infusion, the number of SSO₂ Cartridges used, SSO₂ Cartridge tracking information and total SSO₂ Infusion time, is recorded on the SSO₂ Therapy Procedure case report form.

Concerns related to device performance should be reported immediately to the TherOx, Inc. Clinical Representative and/or TherOx Technical Support at 1-888-2-THEROX or 1-949-757-1999. This service is available 24-hours a day, 7-days a week.

7.3.1.4 Other Procedural Considerations

If an IABP is indicated at any point after initiation of SSO₂ Therapy, prior to the completion of the 90-minute SSO₂ infusion, the SSO₂ infusion must be discontinued.

7.3.1.5 Post Catheterization Laboratory - In-Hospital Procedures

Following treatment, patients will be sent to the CCU, Step-Down Unit, or Coronary Care Floor at the discretion of the investigator.

Patients will receive appropriate therapies (*e.g.*, anticoagulation) according to standard healthcare facility practice. If available during the procedure, the following data should be collected:

- Antiplatelet loading dose
- Stent use attributes (*e.g.*, length, diameter, overlapping, number of stents, type)
- Product performance
- Lesion characteristics (ACC/AHA Classification Scheme of Coronary Lesions)
- Clinical events that occur during the procedure including death, MI, revascularization, and stent thrombosis. Adverse event (AE) data with related laboratory test results, ECG, and subsequent repeat coronary angiography results.
- CK, CK-MB, and/or troponin (collect immediately post-procedure)
- ECG (collect immediately post-procedure)
- Discharge instructions
- Procedural complications (Inability to initiate SSO₂ Therapy, abrupt vessel closure, dissection, no-reflow, etc)

8 ENDPOINT ASSESSMENT

8.1 Clinical Follow-up

Clinical follow-up will occur as a telephone contact or office visit at the following time points:

30 days	7
180 days	14
1 year	30

If a patient completes a clinic visit independent of this protocol and outside the protocol-required follow-up time points, this information will be obtained from the patient's source documents. All efforts must be made to obtain follow-up information on patients who have received study procedures or who have been treated for serious adverse event (SAE) in a non-study-related health care facility.

If available, the following data should be collected at the specified time points:

- Clinical events including death, MI, revascularization, stroke and stent thrombosis at 30, 180 days and at 1 year.
- AE related data including laboratory test results, ECG, and subsequent repeat coronary angiography results, at the time of the event.
- Patient compliance and therapy interruptions with adjunctive antiplatelet therapy and SAE bleeding complications at 30, 180 days and at 1 year.
- Chronic concomitant medication at 30, 180 days and at 1 year

8.1.1 Additional Event-Driven Visits

Additional event-driven visits may occur as clinically warranted. If available, the following data should be collected at these visits:

- Clinical events including death, MI, revascularization, and stent thrombosis. Also, AE related data including laboratory test results, ECG, details, and subsequent coronary angiography results
- Patient compliance and therapy interruptions with adjunctive antiplatelet therapy and major bleeding complications
- Chronic concomitant medication

8.2 Adverse Events

During each clinical follow-up, the investigator or designee will determine AE occurrences. An AE is defined as any untoward medical occurrence in a patient or clinical investigation when the patient was administered a study device which does not necessarily have a causal relationship with this treatment.

An adverse device effect is defined as any untoward and unintended response to a medical device. This definition includes any event resulting from insufficiencies or inadequacies in the IFU, device deployment, and user error.

8.2.1 Serious Adverse Event (SAE)

A SAE is fatal or leads to a serious deterioration in health resulting in the following:

- A life-threatening situation
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- An important medical event that may not result in death, be life-threatening, or require hospitalization but may be considered serious when, based upon appropriate medical judgment, may jeopardize the patient and/or may require intervention to prevent one of the outcomes listed in this definition.

8.2.2 Serious Injury

A serious injury is defined by the following:

- Life-threatening injuries/illnesses
- Injuries/illnesses resulting in permanent impairment of a body function or permanent damage to a body structure
- Injuries/illnesses necessitating medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

Here, “permanent” is defined as irreversible impairment or damage to a body structure or function, excluding trivial impairment or damage.

Collection of AEs begins when procedure starts. Pre-existing conditions are not reported as AEs unless there has been a worsening in severity or frequency which cannot be attributed to the disease’s natural history or progression. Event

description, date of onset, duration, treatment, outcome, and relationship to device will be collected on the AE case report form.

There are no experimental procedures being conducted in this post-approval study. Only approved products are being used according to the IFU and current clinical practice standards.

[TherOx SSO₂ Therapy has not been evaluated in pregnant women]

8.3 Medical Device Reporting

8.3.1 Manufacturer Reporting Requirements

The AO System is commercially available and subject to FDA Medical Device Reporting (MDR) regulations. These regulations require manufacturers who receive complaints of device malfunctions, serious injuries or deaths associated with medical devices to notify FDA of the incident.

TherOx, Inc. will comply with the MDR requirements for devices used in this study through the information gathered on the case report forms and source documents obtained from the investigational site. The collective information required on TherOx, Inc. MDR procedure forms are designed to comply with time sensitive reporting requirements. TherOx, Inc. will submit MDR reports according to 21 CFR parts 803.50 through 803.58.

8.3.2 Clinical Site (User Facility) Reporting Requirements

Death and serious injury reporting is captured on the product performance CRF provided by TherOx, Inc. according to 21 CFR parts 803.30 and 803.32 as follows:

- The User Facility must report when the TherOx DownStream AO device has or may have caused or contributed to a patient death within 10 days of becoming aware of the incident. This User Facility report must be submitted to TherOx, Inc.
- The User Facility must report when the AO System or SSO₂ Therapy has or may have caused or contributed to a patient serious injury within 10 days of becoming aware of the incident. This User Facility report must be submitted to TherOx, Inc.
- The User Facility reports shall include the following information:
 - Patient information
 - AE description or product problem

- Outcomes attributed to the AE, such as death or serious injury that includes any of the following:
 - a) A life threatening injury or illness
 - b) A disability resulting in permanent impairment of a body function or permanent damage to a body structure
 - c) An injury or illness that requires intervention to prevent permanent impairment a body structure or a body function
- Device information
- User facility and initial reporter information

The clinical site (user facility) must fulfill its reporting obligations to FDA regarding these events independently of the protocol-required reporting obligations to the study sponsor.

Throughout the study, TherOx, Inc. will report to FDA on death, myocardial infarction, revascularization, stent thrombosis, SAE bleeding complications, and other serious adverse events in designated post-approval study status reports.

The interim post-approval study status report will normally be submitted every 6 months for the first 2 years of the study and annually thereafter until the final report has been submitted according to Guidance for Industry and FDA staff: Procedures for Handling Post-approval Studies Imposed by PMA Order.

8.4 Event Adjudication

8.4.1 Clinical Events Committee

The CEC is composed of independent interventional cardiologists who are not participating in this study and are not affiliated with TherOx, Inc. The CEC will review and adjudicate according to definitions for the following: death, MI, revascularization, stroke, and stent thrombosis. In addition, the CEC will also review and adjudicate SAE bleeding complications and determine event severity and relationship. See **Section 17.1 Appendix I Definitions** for details.

9 STATISTICAL DESIGN AND ANALYSIS

9.1 Statistical Overview

The purpose of this study is to evaluate the AO System and SSO₂ Therapy continued safety during commercial use in real world settings.

9.2 Analytical Populations

Anterior STEMI patients treated with PCI within 6 hours of symptom onset who receive SSO₂ Therapy as an adjunct to their index procedure. The same analytical population will be used for both the SSO₂ PAS group and the HORIZONS Control group.

9.3 Sample Size Calculations and Assumptions

The patient sample size for this study was derived using the anticipated safety based on the following:

- Composite incidence rate of Major Adverse Cardiac Events (MACE) defined as death, myocardial infarction (MI) and target vessel revascularization at 1 year using a non-inferiority test at $p=0.05$ level with assumed base rates of 10.7% in each arm (control and SSO₂ Therapy) and a 6% proposed safety delta (definition of lack of inferiority). Since the control arm is based on 681 patients obtained from the HORIZONS trial, the base rate of 10.7% was determined from a preliminary evaluation of data from that study.
- 8 % attrition rate over the one year of evaluation (based on the results from the HORIZONS trial)
- Power of 90% and a two-tailed significance level of 5%
- Comparison of the results from the control group (HORIZONS data) and the SSO₂ Therapy group are based on a large-sample (Gaussian or z) test comparing two proportions without correction for continuity

With these assumptions and without accounting for attrition the sample size for the SSO₂ Therapy group is 342 (to be compared with the 681 observations in the HORIZONS trial). However, allowing for the attrition rate of 8%, the sample size will increased by a factor of $1/(1-R)^2$, where R =attrition rate, to 404 (Reference: Piantadosi S. Clinical Trials: A Methodologic Perspective, 2nd edition. Hoboken, NJ: John Wiley and Sons, Inc., 2005, pg. 299-301).

It also is noted that with the given sample size the secondary endpoint of 1 year mortality can be estimated with an exact 95% confidence interval (based on the conservative method of Clopper and Pearson, cf. Clopper CJ, Pearson ES [1934]. The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometrika*, 36, 370) with an expected upper bound of approximately 6.5% (and assuming the mortality rate is on the order of about 2.6% as was found with the HORIZONS data).

9.4 Statistical Analyses

9.4.1 Primary Analysis

The analysis of the primary outcome variable, the 1-year MACE rate, will be based on the large-sample (Gaussian approximation or z) non-inferiority test of two proportions comparing the control data from the HORIZONS study with the results from the SSO₂ Therapy group obtained from the current investigation. The definition of non-inferiority will be a delta of 6%, which is in agreement with the level used in prior studies of SSO₂ Therapy. This analysis will be on an intent-to-treat basis meaning that all patients who receive SSO₂ Therapy will be included in the analysis regardless of whether they complete the one year follow-up period. In order to perform this analysis, patients who are lost-to-follow up or for whatever reason do not complete the primary study period will have their MACE status imputed as described in section 9.4.4.

9.4.2 Secondary Analysis

The MACE rate at 30 and 180 days will be evaluated using the same method as described above but without data imputation for missing results because of the secondary nature of this analysis.

The mortality rate at one year will be evaluated using an exact 95% confidence interval based on the method of Clopper and Pearson. The endpoints of this interval, particularly the upper bound, will be compared with clinically acceptable values for mortality in this patient population to evaluate the acceptability of the outcome.

Stent occlusion event rates at 30 days, 180 days and 1 year will be evaluated through proportions and the use of 95% exact confidence intervals. A similar analysis will be conducted for bleeding events classified as serious. For descriptive purposes, the results for both the SSO₂ Therapy and HORIZONS data groups will be reported in parallel.

For descriptive purposes, the comparability of the study groups at baseline will be compared with regard to demographic characteristics, medical history, disease status, PCI procedure, and other baseline values using t-tests for independent samples for continuous variables and Mantel-Haenszel chi-square test for trends for categorical and rating scale data with limited (short) scales.

Adverse events will be tabulated for the SSO₂ Therapy data based on MedDRA (version 8.1) coding and reported as counts and percentages for the various

categories. Various efficacy variables will be evaluated descriptively for the SSO₂ Therapy group using means, standard deviations, medians and interquartile ranges as appropriate. These variables include reduction in final infarct size measured as a percentage of the left ventricle by 14-day Tc-99m Sestamibi SPECT imaging and ST-segment time trend curve areas evaluated at 0-3, 0-4, and 0-6 hours post-PCI, as well as other clinical outcomes evaluated in the AMIHOT II study.

9.4.3 Other Analysis

Given the post market nature of this study, no formal interim analyses of the study data will be conducted. However, all adverse event and procedural success evaluations will be performed by an independent Clinical Events Committee.

9.5 Procedures to Account for Missing Data

As noted in section 9.4.1, the primary endpoint of the occurrence of a MACE event in the one year follow-up period may be missing for some subjects. As a result, to perform an intent-to-treat analysis, this result will have to be imputed for some patients. We will use a multiple logistic regression imputation model based on data from HORIZONS in order to provide an independent source of information to build this model. Candidate variables for inclusion in the model will be chosen from among the baseline and demographic variables with input from clinicians. However, the stratification variables from AMIHOT II of time to reperfusion and lesion location definitely will be included in the model. Since none of the other variables for evaluation in this study will be evaluated in a comparative fashion, imputation procedures will not be employed in those instances.

10 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator, institution or designee will permit direct access to source data/documents in order for study-related monitoring, audits, IRB review, and regulatory inspections to be performed.

Consenting patients are agreeing to allow TherOx, Inc. or designee access and copying rights to pertinent information in their medical records relevant to study participation. As part of the informed consent, the investigator or designee will

obtain permission for regulatory authorities to review any records identifying patients in this study. TherOx, Inc. will not otherwise release any personal information (refer to **Section 13.3 Confidentiality**).

11 QUALITY CONTROL AND ASSURANCE

11.1 Clinical Site and Investigator Selection

TherOx, Inc. will select qualified investigators with varying interventional cardiology experience at health care facilities with adequate resources to participate in this study. Investigational sites will be selected using combined current assessments of site and investigator qualifications.

11.2 Protocol Deviations

It is the Investigator's responsibility to ensure that there are no deviations from the protocol except in cases of medical emergencies, when the deviation is necessary to protect the life or physical well being of the patient. In the event of any deviation from the protocol, a Protocol Deviation Case Report Form will be completed. The occurrence of protocol deviations will be monitored by the study sponsor for evaluation of Investigator compliance to the protocol, Good Clinical Practice (GCP), and regulatory requirements. The Investigator will inform the IRB of all protocol deviations according to the requirements of each reviewing IRB.

The protocol deviations for this protocol consists of, but not limited to, the following:

- Failure to obtain patient's informed consent prior to any study-related activities and the index procedure
- Failure to conduct protocol-required clinical follow-ups within specified time windows
- Failure to report serious adverse events according to protocol requirements

In the event of any deviation from the protocol, the Investigator will be notified of the site's non-compliance. Corrective actions will be required if necessary. Continued protocol deviations despite re-education of study site personnel or persistent protocol deviations may result in termination of the site's study participation. In the event of investigational site enrollment cancellation, patients already enrolled at these sites will continue to be followed per protocol guidelines.

11.3 Training

TherOx Inc. will be responsible for providing training to the investigator and appropriate clinical site personnel. It is recommended that investigators review the IFU.

11.3.1 Monitor Training

TherOx, Inc. and/or designated monitors will be trained appropriately to monitor study progress including but not limited to the protocol and CRFs.

11.4 Good Clinical Practice Compliance

The trial will be conducted in compliance with the protocol, Good Clinical Practices and applicable regulatory requirements.

11.5 Study Monitoring

11.5.1 Site Monitoring

A study specific monitoring plan will be conducted to ensure protocol compliance and applicable regulatory requirements.

11.5.2 Compliance Assessments

TherOx, Inc. or designee may conduct periodic compliance assessments at various study sites. TherOx, Inc. or designee may request access to all trial records including source documentation for inspection and duplication during a compliance assessment. The site investigator and research coordinator must be available to respond to reasonable requests and queries made during the compliance assessment process.

11.5.3 Regulatory Agency Inspection

In the event that an investigator is contacted by a regulatory agency regarding this trial, the investigator will notify TherOx, Inc. immediately. The site investigator and research coordinator must be available to respond to reasonable requests and queries made during the inspection process. The investigator must provide TherOx, Inc. or designee with copies of all correspondence that may impact review of the current trial (*e.g.*, Form FDA 483, Inspectional Observations, and Warning Letters). TherOx, Inc. may provide needed assistance in responding to regulatory audits.

11.6 Committees

11.6.1 Executive Committee

The Executive Committee may be composed of Principal Investigators and TherOx, Inc.'s Director of Clinical Operations and Regulatory Department representative. This committee will oversee general aspects of the study including final protocol review, ongoing general data collection monitoring, and review of implementation and/or operational issues that may arise and warrant a protocol amendment or other corrective action. The Executive Committee will also approve policy regarding presentations and/or publications.

11.6.2 Operations Committee

The Operations Committee is a TherOx Inc. designated team composed of clinical research representatives that will be responsible for daily administrative trial management. This committee will monitor patient enrollment, clinical site progress, and protocol compliance. The committee will also provide assistance to sites with trial management issues, including compliance with specific record keeping and reporting requirements.

11.6.3 Publication Committee

The Publication Committee is composed of representatives from TherOx, Inc. Clinical Research department, investigators, and other personnel as determined and approved by the Executive Committee. This team will oversee presentation and/or publication aspects of the post-approval study. The Publication Committee will determine policy and strategies regarding individual presentations and/or publications arising from study-generated data. The committee will also review all external requests for accessing study-related data and strategies aligning with TherOx, Inc. presentation and publication team expectations. The committee will also follow TherOx, Inc. applicable policies and standard operating procedures.

12 DATA HANDLING AND RECORDKEEPING

For the study duration, the investigator will maintain complete and accurate documentation including but not limited to the following: medical records, study progress records, laboratory reports, case report forms, signed informed consent forms, device serial numbers for monitoring malfunctions, correspondence with the IRB and the study sponsor and designated representatives, AE reports, and information regarding patient discontinuation or study completion. Data from the HORIZONS study are maintained by the Cardiovascular Research Foundation (CRF).

12.1 Source Documentation

The following materials should be included in the patient record:

- Patient medical history/physical condition prior to study involvement
- Dated and signed notes on the day of entry into the study referencing TherOx, Inc., protocol number, site and patient ID number, and a statement that confirms informed consent
- Dated and signed notes from each patient's visit (for specific results of procedures and exams)
- AEs reported and their outcome including supporting documents
- Patient's condition upon study completion or withdrawal

12.2 Case Report Form Completion

Accurate primary data collection will be performed by research coordinators at each clinical site trained on the protocol and case report form completion. TherOx, Inc. or designee will provide clinical monitoring to include case report form review and parity checks with the source documentation, including operator worksheets retained with case report form documentation and health care facility charts.

12.3 Record Retention

The Primary Investigator should maintain all records pertaining to this study for 2 full years following study completion or as otherwise instructed by TherOx, Inc. TherOx, Inc. will maintain copies of correspondence, data, monitoring reports and other relevant clinical study records.

13 ETHICAL CONSIDERATIONS

13.1 Institutional Review Board Review

Institutional Review Board approval for the protocol and informed consent form will be obtained by the investigator prior to study participation. The approval letter must be signed by the IRB Chairperson or authorized representative prior to beginning this study and a copy must be provided to TherOx, Inc. No changes will be made to the protocol or informed consent form without appropriate approval from the IRB, TherOx, Inc. and/or the regulatory agencies. Additionally, the Primary Investigator or representative will provide an IRB membership list or assurance number to TherOx, Inc.

According to IRB requirements, the investigator will report study progress until it is completed. Further, any protocol amendments as well as associated informed consent changes will be submitted to the IRB and written approval must be obtained prior to implementation.

13.2 Informed Consent

All patients or legally authorized patient representatives must sign a current IRB-approved informed consent form prior to any study-related activities and the index procedure. Failure to obtain signed informed consent will render the patient ineligible for the study. All enrolled patients will sign a consent form that has been approved by both TherOx, Inc. and the IRB. The signed informed consent will be kept in the patient's medical records and a copy given to the patient or legally authorized patient representative. The consent form or a separate authorization form will include language that satisfies the Health Insurance Portability and Accountability Act of 1996 (45 CFR Parts 160 and 164) and associated regulations.

13.3 Confidentiality

To ensure compliance with the Health Insurance Portability and Accountability Act of 1996, confidentiality of protected health information shall be maintained by all parties involved at all times throughout the clinical trial. All data will be secured against unauthorized access.

13.4 Submitting Reports

TherOx, Inc. will submit interim post-approval study reports to FDA every 6 months for the first 2 years of the study and annually thereafter until the final post-approval study report has been submitted. Annual clinical updates will be sent to investigators.

14 PROTOCOL AMENDMENTS

Approved protocol amendments will be provided to investigators by TherOx, Inc. prior to implementation. The site Primary Investigator will be responsible for notifying the IRB of the protocol amendment with administrative changes or obtaining IRB approval of the protocol amendment with changes in patient care or safety, according to instructions provided by TherOx, Inc. with the protocol amendment. Institutional Review Board acknowledgements/approvals must be documented in writing prior to implementing protocol amendments. Copies of this documentation must also be provided to TherOx, Inc.

15 TERMINATION OF STUDY SITE PARTICIPATION

TherOx, Inc. reserves the right to terminate study site participation and remove appropriate study materials at any time. Specific instances that may precipitate such termination include but are not limited to the following:

- Failure to meet minimum patient enrollment requirements
- Failure to comply with protocol specified procedures and documentation
- Failure to comply with Good Clinical Practice

The site Primary Investigator may also discontinue study participation with suitable written notice to TherOx, Inc.

16 PUBLICATION POLICY

Study derived data are the sole property of TherOx, Inc. Investigators will not use study-related data without written consent from TherOx, Inc. for any purpose other than study completion or for generating publication material as stated in the study site agreement. The presentation and/or publication of results from a single study site cannot precede presentation and/or publication of multi-center results and must be approved by the Publication Committee. TherOx, Inc. acknowledges that the Principal Investigators intend to publish a multi-center publication regarding the aggregate study results prepared in accordance with the study statistical analysis plan. Proposed presentation and/or publication materials must be received at least 60 days prior to the proposed submission date to be reviewed by TherOx, Inc. for compliance with the publication policy stated in study site agreement. Exceptions to this timeline must be approved by the Executive Committee.

17 APPENDICES

17.1 Appendix I: General Adverse Event Classifications and Definitions

ADVERSE EVENT: Any undesirable experience that is a deviation from the baseline status (sign, symptom, illness, abnormal laboratory value, or other medical event) occurring to a subject during the course of the study, whether or not it is related to the devices or procedures described in the Investigational Plan.

SERIOUS ADVERSE EVENT: Any adverse event occurring to a subject during the course of the study that is fatal, life-threatening, disabling, results in patient hospitalization or prolongation of hospitalization, or requires medical intervention to prevent permanent impairment of a body structure or function.

ADVERSE EVENT ATTRIBUTION: Adverse events will be assigned an attribution according to the believed primary cause. Events will be categorized by relationship to SSO₂ Therapy devices (system/cartridge), SSO₂ Therapy procedure, index PCI procedure, study medications, coronary artery disease, other comorbid condition, or other.

Attribution of Event

SSO₂ Device: The clinical event has a reasonable time sequence to use of the SSO₂ Therapy devices (*i.e.*, system, cartridge or infusion catheter) and is unlikely to be attributed to concurrent disease or other interventional procedures or medications. It is reasonable to believe that the device directly caused or contributed to the adverse event.

SSO₂ Procedure: It is reasonable to believe that the event is associated with the SSO₂ procedure rather than specifically the SSO₂ devices, interventional procedures, concurrent disease, or medications. Other products or medications required specifically for the SSO₂ procedure (*e.g.*, extended anticoagulation regimen, arterial sheath manipulation) are likely to have contributed to the occurrence of the event.

PCI Procedure: It is reasonable to believe that the event is associated with the patient's index PCI procedure in general and is not specific to the SSO₂ devices, SSO₂ Therapy procedure, concurrent disease, or medications. Example: vessel dissection noted after PCI and prior to initiation of SSO₂ Therapy.

Study Medications: It is reasonable to believe that the event is associated with the study medications required and is not otherwise specific to the SSO₂ devices, SSO₂ Therapy procedure, index PCI procedure, or concurrent disease (*e.g.*, bleeding associated with Clopidogrel).

Coronary Artery Disease: It is reasonable to believe that the event is associated with the patient's coronary artery disease in general and is not specific to the SSO₂ devices, SSO₂ Therapy procedure, index PCI procedure, or study medications.

Comorbid Condition: It is reasonable to believe that the event is directly associated with progression of another pre-existing condition/co-morbidity (not coronary artery disease). Pre-existing conditions that are aggravated or become more severe during or after the procedure should be evaluated on a case-by-case basis to determine if the event may be more appropriately classified as SSO₂ device-related or SSO₂ Therapy procedure-related.

Unknown: The adverse event cannot be assigned attribution because information is insufficient or contradictory, and cannot be supplemented or verified.

ADVERSE EVENT IDENTIFICATION: a condition that is one of the following:

- a) A unique symptom or event that is a change from the patient's baseline status.
- b) A series of symptoms or events that can be categorized as a single entity based on definitions found herein.
- c) A specific diagnosis responsible for a clinical change

NOT AN EVENT: Reported events that are symptoms associated with another reported event, duplicate events identified using similar or different nomenclature reported with the same start/stop dates or events represents observations or incidental findings or determined to be inaccurately/incorrectly reported.

- a. **OBSERVATION/ INCIDENTAL FINDING:** Abnormal or non-specific findings/observation that may be associated with study activities but has no identifiable clinical correlates and suggests no specific pathophysiological process – such as “painful access” or “tired”. Such events will not be considered to be an adverse event unless associated with clinical sequelae or requiring specific intervention. When clinical sequelae occur or when the intervention required exceeds standard response for similar symptom/event, it will be reported as an adverse event.

REQUIRES MORE INFORMATION TO FINALIZE: An adverse event where more data is essential for a proper assessment or the additional data are under examination.

I. PRIMARY SAFETY ENDPOINT DEFINITIONS:

MAJOR ADVERSE CARDIAC ADVENTS (MACE): Defined as death, reinfarction, stroke, target vessel revascularization within 30 days or prior to hospital discharge.

STUDY SPECIFIC MACE (30-DAY OR HOSPITAL DISCHARGE)

DEATH: Including all deaths by any cause occurring from time of randomization through 30 days or until hospital discharge, whichever is later.

REINFARCTION: Presence of recurrent ischemic symptoms thought to be of cardiac origin of at least 20 minutes duration and redevelopment of ST-Segment elevation in two or more contiguous precordial leads and/or worsening of existing Q waves or development of new pathologic Q waves in the precordial leads. For defining reinfarction occurring 96 hours or more after the index event, reelevation of CK-MB isoenzyme may be utilized as a substitute for ST segment changes. Note: degree of ST change cannot be stipulated during periprocedural phase because it may be related to underlying persistent ST segment changes related to presentation event. Reinfarction events occurring within the 30-day (or hospital discharge) MACE window will be considered primary safety endpoint events if they occur in the region of the originally treated infarct location.

STROKE: Neurological deficit lasting 24 hours or longer, or lasting less than 24 hours with a brain imaging study showing infarction. Stroke events occurring within the 30-day (or hospital discharge) MACE window will be considered primary safety endpoint events.

TARGET VESSEL REVASCULARIZATION (TVR): Revascularization of AMIHOT II study-related vessel by means of PCI or CABG. Target Vessel Revascularization events occurring within the 30-day (or hospital discharge) MACE window will be considered primary safety endpoint events. Any intervention performed in the cath lab at the time of treatment will *not* be considered a TVR.

II. CLINICAL ADVERSE EVENT CLASSIFICATIONS:

1. CARDIAC DEFINITIONS

ABRUPT CLOSURE: Defined as the occurrence of new severely reduced flow (TIMI flow grade 0 or I) within the target vessel that persisted and required rescue by a non-assigned treatment strategy (including emergency surgery), or resulted in myocardial infarction or death. Abrupt closure requires proven association with a mechanical dissection of the treatment site or instrumented vessel, coronary thrombus or severe spasm. Abrupt closure does not connote "no reflow" (due to microvasculature limitation), in which the epicardial artery is patent but had reduced flow. Abrupt closure also does not connote transient closure with reduced flow in which the index treatment application reversed the closure.

SUBACUTE THROMBOSIS: Defined as abrupt closure that occurred after the index procedure is completed (and the patient left the catheterization laboratory) and before the 30-day follow-up endpoint.

THREATENED ABRUPT CLOSURE: Defined as a grade B dissection and > 50% diameter stenosis or any dissection of grade C or higher.

DISTAL EMBOLIZATION: Defined as a new abrupt cut off or filling defect distal to the treated lesion in either the distal target vessel or associated branches.

NO REFLOW: Defined as sustained or transient reduction in antegrade flow that is not associated with an obstructive lesion at the treatment site.

PERFORATION: Perforations are classified as follows:

Angiographic perforation: Perforation detected by the clinical site to the core laboratory at any point during the procedure.

Clinical perforation: Perforation requiring additional treatment (including efforts to seal the perforation or pericardial drainage), or resulting in significant pericardial effusion, abrupt closure, myocardial infarction, or death.

Cardiac tamponade: Perforation resulting in cardiac tamponade

**DISSECTION, NHLBI (National Heart, Lung and Blood Institute)
CLASSIFICATION:**

Type A: Small radiolucent area within the lumen of the vessel disappearing with the passage of the contrast material.

Type B: Appearance of contrast medium parallel to the lumen of the vessel disappearing within a few cardiac cycles.

Type C: Dissection protruding outside the lumen of the vessel persisting after passage of the contrast material.

Type D: Spiral shaped filing defect with or without delayed run-off of the contrast material in the antegrade flow.

Type E: Persistent luminal filing defect with delayed run-off of the contrast arterial in the distal lumen.

Type F: Filing defect accompanied by total coronary occlusion.

CORONARY VASOSPASM: Transient narrowing > 50% diameter in a region where a < 25% diameter stenosis had previously been.

CARDIAC ARRHYTHMIA: Includes any deviation reported from normal sinus rhythm including but not limited to sinus tachycardia, sinus bradycardia, or atrial fibrillation.

Documentation of any one of the following requiring cardioversion, IV antiarrhythmics and/or permanent pacemaker implant:

- a) **Atrial Fibrillation:** New onset of atrial fibrillation/flutter (AF).
- b) **Other Supraventricular Tachyarrhythmia:** requiring treatment.
- c) **Heart Block:** New heart block requiring the implantation of a temporary or permanent pacemaker prior to discharge.
- d) **Sustained VT or VFIB:** Requiring cardioversion and/or anti-arrhythmic therapy and/or permanent defibrillator implantation.
- **Bradycardia:** HR < 50
- **Tachycardia:** HR > 120

Serious: Requiring cardioversion or anticoagulation, or associated with an embolic event

Nonserious: Converted with meds or spontaneously

CARDIAC ARREST: Absent or inadequate contraction of the left ventricle of the heart that immediately causes body wide circulatory failure.

CARDIOGENIC SHOCK: Patient presents with SBP < 80 mm Hg for more than 30 minutes unresponsive to fluids or requiring intravenous pressors or an IABP.

CABG: Coronary artery bypass graft surgery classified as emergent, urgent, or elective as follows:

Elective: The patient is clinically stable and the overall medical condition does not indicate the need for revascularization within 48 hours.

Urgent: The patient is clinically unstable and the condition warrants revascularization within 2-48 hours

Emergent: The patient is clinically unstable and the condition requires immediate revascularization within 2 hours.

RECURRENT MI: Presence of recurrent ischemic symptoms thought to be of cardiac origin of at least 20 minutes duration and redevelopment of ST-Segment elevation in two or more contiguous precordial leads and/or worsening of existing Q waves or development of new pathologic Q waves in the precordial leads. For defining reinfarction occurring 96 hours or more after the index event, reelevation of CK-MB isoenzyme may be utilized as a substitute for ST segment changes. Note: degree of ST change cannot be stipulated during periprocedural phase because it may be related to underlying persistent ST segment changes related to presentation event. Recurrent MI events will be divided into the following categories: Infarction in the region of the originally treated infarct OR Recurrent MI in a region remote from the originally treated infarct.

ANGINA: A tight or heavy feeling in the chest, discomfort which spreads from the chest to the arm, back, neck, jaw, or stomach, numbness or tingling in the shoulders, arms or wrists, shortness of breath, and nausea.

UNSTABLE ANGINA: Angina which increases in frequency, intensity, or duration, which occurs at rest, or which is new in onset. Unstable angina is a syndrome that is intermediate between stable angina and myocardial infarction: it is characterized by an accelerating or "crescendo" pattern of chest pain that lasts longer than in stable angina, occurs at rest or with less exertion than in stable angina, or is less responsive to medication. Unstable angina and myocardial infarction are considered acute coronary syndromes.

MYOCARDIAL ISCHEMIA: Lack of blood supply to the heart muscle due to a narrowing of the coronary arteries. Myocardial ischemia will be utilized to document the diagnosis when any of the following are reported without symptoms of angina and not diagnosed as myocardial infarction: positive stress test, ischemic EKG changes, revascularization based on an imaging study result

CONGESTIVE HEART FAILURE: Documentation of one of the following: a) Paroxysmal nocturnal dyspnea (PND), b) Dyspnea on exertion (DOE) due to heart failure, c) elevated PCW with associated SOB or x-ray consistent with congestion. May be related to **fluid overload in the presence of underlying cardiovascular disease.**

HYPERTENSION: Systolic BP > 140 mmHg, or diastolic >90 mmHg, or requiring specific medical therapy.

HYPOTENSION: Any prolonged systolic blood pressure < 80 mmHg associated with symptoms and requiring intravenous vasopressor medications.

RESTENOSIS: 50% or greater diameter stenosis in a previously successfully treated lesion as demonstrated by angiographic imaging.

CORONARY ARTERY PERFORATION/RUPTURE: Perforations are classified as follows:

Angiographic perforation: Perforation detected by the clinical site or the core laboratory at any point during the procedure.

Clinical perforation: Perforation requiring additional treatment (including efforts to seal the perforation), or resulting in significant extravasation of blood from the site, abrupt closure, MI, or death.

CARDIAC TAMPONADE: Acute compression of the heart which is due to effusion of the fluid into the pericardium or mediastinum or to the collection of blood or other fluid in the pericardium from rupture of the heart or penetrating trauma which compromises cardiac filling, and requires intervention. This should be documented by either:

- a) echo showing pericardial fluid and signs of tamponade such as right heart compression, or
- b) systemic hypotension due to the suspected or confirmed presence of pericardial fluid compromising cardiac function
- c) mediastinal compression

1. NEUROLOGIC DEFINITIONS:

STROKE: Neurological deficit lasting 24 hours or longer, or lasting less than 24 hours with a brain imaging study showing infarction. Stroke events occurring within the 30-day (or hospital discharge) MACE window will be considered primary safety endpoint events.

TRANSIENT ISCHEMIC ATTACK (TIA): Neurological deficit lasting less than 24 hours and, if an imaging study is performed, shows no evidence of infarction.

SEIZURE: An abrupt neurological change with cognitive or sensorimotor signs such as tonic/clonic activity consistent with an underlying a process related to abnormal electrical discharges in the brain.

COMA: Neurological unresponsiveness not due to medications or metabolic causes. Prolonged coma is one that persists for greater than **24 hrs.**

DECLINE IN COGNITION: A change in mental status of an etiology other than stroke. This includes nonfocal behavioral, mutational or alertness changes.

PARALYSIS: Localized or generalized loss of muscle function secondary to neurologic damage.

3. SAE BLEEDING DEFINITIONS:

HEMORRHAGE (categorized by severity): Any bleeding which results in a drop in hematocrit from pre-procedure level of greater than or equal to 6 points (2 grams of hemoglobin) or a hematocrit <30, or blood loss that requires transfusion or results in substantial hemodynamic compromise requiring treatment.

- **Severe/Life Threatening Bleeding:** Bleeding that is intracranial or that results in substantial hemodynamic compromise requiring treatment.
- **Moderate Bleeding: bleeding requiring transfusion** defined as any blood loss requiring transfusion of blood products.
- **Mild Bleeding:** Bleeding that does not require transfusion or result in hemodynamic compromise.

Intracranial Hemorrhage: Includes all bleeding within the cranium either Subarachnoid, intra-parenchymal, or intracerebral.

HEMATOMA: Collection of blood (or serous fluid) at the operative site which exceeds 5 cm or requires treatment (surgical intervention, injection therapy, compression therapy) or prolongs hospitalization.

VASCULAR DAMAGE:

DISSECTION: Presence of angiographically evident intimal disruption (e.g., linear luminal density or luminal staining or linear intraluminal filling defect) which requires treatment.

PERFORATION/ RUPTURE: Any angiographic evidence of transmural vessel tears with extravasation of contrast media outside the lumen of the vessel.

ARTERIOVENOUS FISTULA: A traumatic communication between an artery and vein documented by ultrasound or angiography

PSEUDOANEURYSM: Compartmentalized blood contiguous with arterial lumen documented by ultrasound or visualized at repair.

ARTERIAL OCCLUSION/THROMBOSIS AT PUNCTURE SITE:
Angiographic or ultrasonographic evidence of occlusion at the puncture site

DEEP VEIN THROMBOSIS: Angiographic or ultrasonographic evidence of thromboembolic occlusion in the lower extremities, other than minor peripheral occlusions.

RETROPERITONEAL HEMORRHAGE: Bleeding into the retroperitoneum characterized by signs such as hypotension, decreasing hemoglobin, abdominal distention, peritoneal signs, flank and/or hip pain, and increasing bruising.

HEMOLYSIS: The breakdown of red blood cells resulting in elevated amounts of free hemoglobin into the circulation.

EMBOLISM (including air emboli and thromboemboli): The blockage of a blood vessel by an embolus, which can include a thrombus or an air bubble.

PERIPHERAL ISCHEMIA: Deficient supply of blood to the blood vessels outside the heart and brain that is due to obstruction of the inflow of arterial blood.

PERIPHERAL VASCULAR DISORDER: Vascular diseases affecting blood vessels located outside the heart and brain, especially those vessels supplying the extremities;

THROMBOPHLEBITIS: Inflammation of a vein with formation of a thrombus.

4. RESPIRATORY/PULMONARY DEFINITIONS:

PULMONARY EDEMA: An abnormal accumulation of fluid in the lung tissues

PULMONARY EMBOLISM: Pulmonary embolism diagnosed by study such as V/Q scan or angiogram or spiral CT or clinical symptoms consistent with PE in the absence of these studies that result in treatment.

RESPIRATORY COMPLICATIONS: Includes prolonged intubation, need for tracheostomy, and/or ventilator dependence.

RESPIRATORY ACIDOSIS: Reduced alkalinity of the blood and tissues caused by excessive retention of carbon dioxide due to a respiratory abnormality.

RESPIRATORY FAILURE: New onset of respiratory insufficiency that requires placement of chest tube, bronchodilators, or ventilatory support.

5. GASTROINTESTINAL/GENITOURINARY DEFINITIONS

RENAL COMPLICATIONS:

Renal Failure: Inability of the kidneys to filter toxins resulting in a serum creatinine increase to > 2.0 mg/dl and one of the following:

- increase of 2.0 mg/dl in serum creatinine over any previous value
- 50% or greater increase in creatinine over baseline procedural value
- requirement for dialysis

Renal Insufficiency: An increase in serum creatinine of ≥ 1.0 mg/dl over previous value

OLIGURIA: Urine output between 100-500mL within 24 hour period.

ANURIA: Urine output less than 100mL within 24 hour period.

ANURESIS (Urinary Retention): Urination impossible despite full bladder requiring prolonged catheterization (> 4 days) or repeat catheterization.

6. BLOOD AND LYMPHATIC DISORDER DEFINITIONS

ANEMIA: Hematocrit decrease from baseline (without bleeding) of greater than or equal to 6 points (2 grams of hemoglobin) or one which does not remain above 30%, or is associated with hemodynamic changes or requires intervention (e.g. transfusion). Hematocrit drops with no bleeding that do not require intervention will be considered incidental findings.

THROMBOCYTOPENIA: A persistent decrease in the number of blood platelets.

HIT (HEPARIN INDUCED THROMBOCYTOPENIA): Low blood platelet count as a result of the medication heparin.

DISSEMINATED INTRAVASCULAR COAGULATION: A syndrome arising as a complication of many different serious and life-threatening illnesses. In its acute form it is a hemorrhagic disorder, characterized by multiple ecchymoses, mucosal bleeding, and depletion of platelets and clotting factors. Chronic DIC, is more subtle and involves thromboembolism accompanied by evidence of activation of the coagulation system.

7. INFECTIOUS/INFLAMMATORY DEFINITIONS:

ALLERGIC REACTION: An allergic reaction characterized by rash, nausea, vomiting, upper respiratory congestion, urticaria, shortness-of-breath, vasovagal reaction, or general collapse (anaphylaxis).

INFECTION: Culture-proven infections or presumptive treatment with antibiotics for clinically diagnosed infection not at catheter insertion site.

PNEUMONIA: Pneumonia diagnosed by one of the following: Positive cultures of sputum, blood, pleural fluid, emphysema fluid, transtracheal fluid or transthoracic fluid; consistent with the diagnosis and clinical findings of pneumonia. Should include chest x-ray diagnostic of pulmonary infiltrates.

INFECTION AT CATHETER INSERTION SITE: Culture-proven wound infection or presumptive treatment with antibiotics for clinically diagnosed wound infection.

BACTEREMIA: Presence of viable bacteria in the circulating blood.

SEPSIS: Culture-proven sepsis or presumptive treatment with antibiotics for clinically diagnosed sepsis.

URINARY TRACT INFECTION: Positive urine cultures requiring antibiotic therapy.

VIRAL ILLNESS: Diseases caused by a virus, including Bronchitis, Sinusitis, Cellulitis, and Upper Respiratory Infection.

8. OTHER ADVERSE EVENT DEFINITIONS:

NON-ISCHEMIC CHEST PAIN: Any discomfort in the chest, shoulder, back or chest wall for which a cardiac ischemic origin is ruled out or not suspected. May be cardiac (for example pericardial) or non-cardiac (for example gastrointestinal) in origin.

ANXIETY: A psychiatric disorder causing feelings of mental discomfort, for example, panic disorder, post-traumatic stress disorder or depression

DIZZINESS: Imprecise term commonly used to describe various symptoms such as faintness, giddiness, imbalance, lightheadedness, unsteadiness, or vertigo

NAUSEA: The unsettling feeling in the stomach that accompanies the urge to vomit

VOMITING: The ejection of matter from the stomach in retrograde fashion through the esophagus and mouth.

HEADACHE: A term used to describe aching or pain that occurs in one or more areas of the head, face, mouth, or neck. Headache can be chronic, recurrent, or occasional. The pain can be mild or severe enough to disrupt daily activities.

FATIGUE/MALAISE: Weariness, tiredness, or lack of energy. Generalized feeling of discomfort, illness, or lack of well-being.

PAIN AT CATHETER INSERTION SITE: Pain at the catheter insertion site determined to be associated with the device or procedure and graded as mild, moderate or severe.

FEVER: A temperature > 101°F not related to a culture positive infection.

DRUG REACTIONS: An unwanted or harmful side effect experienced following the administration of a drug or combination of drugs and is suspected to be related to the drug.

PAIN: Reports of pain, ranging from mild discomfort to acute agony, may be generalized or localized, requiring treatment or intervention.

III. OTHER STUDY DEFINITIONS

ANTERIOR MYOCARDIAL INFARCTION: Defined as MI with ST-segment elevation ≥ 1 mm in two or more contiguous leads between V1 and V4 or new left bundle branch block (LBBB) with documentation of LAD system culprit lesion.

SuperSaturated Oxygen (SSO₂) Solution: A solution in which saline for injection is mixed with hyperbaric levels of oxygen in a specialized cartridge.

SSO₂ THERAPY: A 90-minute infusion of hyperoxemic blood into the infarct-related artery post-PCI.

CRF: Case Report Form: The documents designed for the recording of all relevant patient and device related data.

CLINICAL SUCCESS: Defined as device success with no procedural events.

DE NOVO LESION: Defined as a lesion not previously treated.

SSO₂ THERAPY SUCCESS: Defined as successful delivery of SSO₂ Therapy to the target vessel for 90 minutes.

LESION CLASS (American College of Cardiology/American Heart Association Class):

Type A Lesion: Minimally complex, discrete (length < 10 mm), concentric, readily accessible, non-angulated segment (<45 degrees), smooth contour, little or no calcification, less than totally occlusive, not ostial in location, no major side branch involvement, and an absence of thrombus.

Type B Lesions: Moderately complex, tubular (length 10 to 20 mm), eccentric, moderate tortuosity of proximal segment, moderately angulated segment (> 45 degrees, < 90 degrees), irregular contour, moderate or heavy calcification, total occlusions < 3 months old, ostial in location, bifurcation lesions requiring double guidewires, and some thrombus present.

Type C Lesions: Severely complex, diffuse (length > 2 cm), excessive tortuosity of proximal segment, extremely angulated segment > 90 degrees, total occlusions > 3 months old and/or bridging collaterals, inability to protect major side branches, and degenerated vein grafts with friable lesions.

LESION CHARACTERISTICS:

Anastomotic: Lesion located at the junction of a bypass graft and native vessel.

Aneurysm: An expansion of the lumen in the region of maximum stenosis that extends with a wide or narrow mouth beyond the apparent normal contour.

Bifurcation: Lesion located at the origin, or branch of a medium or large diameter vessel.

Eccentricity: A stenosis that has one of its luminal edges in the outer one-quarter of the apparent normal lumen.

Calcification: Readily apparent densities noted within the apparent vascular wall at the site of the stenosis. Calcification is classified as none/mild, moderate when densities noted only during the cardiac cycle prior to contrast injection, and severe when densities noted without cardiac motion prior to contrast injection generally involving both sides of the arterial wall.

Intimal Flap: Extrusion of tissue extending from the arterial surface into the lumen.

Irregularity: Lesion borders with abnormal margins based on the presence of an ulceration, aneurysm, or intimal flap.

Length: "Shoulder to shoulder" distance measured from the proximal shoulder to the distal shoulder of a lesion in the projection that shows the most elongated view of the stenosis.

Discrete: Lesion length < 10 mm.

Tubular/Focal: Lesion length \geq 10 mm and \leq 20 mm.

Diffuse: Lesion length \geq 20 mm.

Location: Designated as ostial, proximal, mid and distal.

Ostial: Lesions that begin within 3 mm of the origin of the artery.

Ulceration: A small crater or flap in a lesion. A discrete lumen widening with a narrow mouth in an area of a stenosis, which may extend beyond the normal arterial lumen.

MYOCARDIAL BLUSH: Angiographic contrast opacification of the myocardial bed subtended by the infarct artery.

MYOCARDIAL BLUSH SCORE:

Blush 0: Absent opacification.

Blush 1: Minimal contrast opacification.

Blush 2: Reduced but clearly evident blush in the infarct zone compared to the ipsilateral, or contralateral non-involved epicardial vessel(s).

Blush 3: Myocardial contrast filling equal to or greater than seen in the non-involved epicardial vessel(s).

MYOCARDIAL INFARCTION (Index):

Ischemic symptoms thought to be of cardiac origin of at least 20 minutes duration

AND ST segment elevation of greater than or equal to 1 mm in 2 or more contiguous leads.

NOTE: Biomarker values should be obtained to confirm diagnosis; however enrollment should not be delayed pending these values.

Myocardial infarction will be categorized according to the following definitions and reported separately.

Q wave MI: development of new, pathological Q waves in 2 or more contiguous leads (as assessed by ECG).

Non-Q wave MI: Absence of pathological Q waves (as assessed by ECG).

PROCEDURAL SUCCESS: Defined as the achievement of a final diameter stenosis of < 50% angiographically using any percutaneous method, without the occurrence of 30 day or in-hospital MACE.

RESTENOTIC LESION: Defined as lesion in a vessel that had undergone a prior percutaneous treatment.

TIMI FLOW:

TIMI 0: Dye fails to enter the microvasculature. There is either minimal or no ground glass appearance ("blush") or opacification of the myocardium in the distribution of the culprit artery indicating lack of tissue level perfusion.

TIMI I: Dye slowly enters but fails to exit the microvasculature. There is the ground glass appearance ("blush") or opacification of the myocardium in the distribution of the culprit lesion that fails to clear from the microvasculature, and dye staining is present on the next injection (approximately 30 seconds between injections).

TIMI II: There is delayed entry and exit of dye from the microvasculature. There is the ground glass appearance ("blush") or opacification of the myocardium in the distribution of the culprit lesion that is strongly persistent at the end of the washout phase (i.e. dye is strongly persistent after 3 cardiac cycles of the washout phase and either does not or only minimally diminishes in intensity during washout).

TIMI III: There is normal entry and exit of dye from the microvasculature. There is the ground glass appearance ("blush") or opacification of the myocardium in the distribution of the culprit lesion that clears normally, and is either gone or only mildly/moderately persistent at the end of the washout phase (i.e. dye is gone or is mildly/moderately persistent after 3 cardiac cycles of the washout phase and noticeably diminishes in intensity during the washout phase), similar to that in an uninvolved artery. Blush that is of only mild intensity throughout the washout phase but fades minimally is also classified as grade III.

THROMBUS: Discrete, mobile intraluminal filling defect with defined borders with or without staining.

TOTAL OCCLUSION: Lesion with TIMI 0 or TIMI I flow.

UNSTABLE ANGINA: Angina which increases in frequency, intensity, or duration, which occurs at rest, or which is new in onset.

VESSEL CHARACTERISTICS:

Angulation: Vessel angle formed by the centerline through the lumen proximal to the stenosis and extending beyond it and a second centerline in the straight portion of the artery distal to the stenosis measured in a non-foreshortened view.

Spasm: Transient narrowing > 50% diameter in a region where a < 25% diameter stenosis had previously been.

Tortuosity: Number of bends that must be traversed by a device to reach the target lesion.

Haziness: Presence of radiolucencies within the arterial lumen not satisfying the criteria for thrombus.

TREATMENT OF EVENTS:

EMERGENT OR URGENT PERCUTANEOUS CORONARY INTERVENTION (PCI):

Urgent: the patient is clinically unstable and the condition warrants revascularization within 24 hours

Emergent: the patient is clinically unstable and the condition requires immediate revascularization.

CABG: Coronary artery bypass graft surgery classified as emergent, urgent, or elective as follows:

Elective: the patient is clinically stable and the overall medical condition does not indicate the need for revascularization within 48 hours.

Urgent: the patient is clinically unstable and the condition warrants revascularization within 2-48 hours

Emergent: the patient is clinically instable and the condition requires immediate revascularization within 2 hours.

SUCCESS DEFINITIONS:

Technical Success: The successful delivery of a minimum of 80 minutes of AO Therapy within 120 minutes with the use of no more than two cartridges.

Procedural Success: Achievement of a final diameter stenosis of < 50% as assessed by angiographic core laboratory using any percutaneous method without the occurrence of any death, stroke or reinfarction (based on ST Segment) during the index procedure.

Clinical Success: Achievement of procedural success without MACE through hospital discharge.

17.2 Appendix II: Acronyms and Abbreviations

% DS	Percent Diameter Stenosis
ABG	Arterial Blood Gas
ACC	American College of Cardiology
ACE	Angiotension Converting Enzyme
ACT	Activated Clotting Time
AE	Adverse Event
AHA	American Heart Association
ALT	Alanine Aminotransferase
AMI	Acute Myocardial Infarction
AMIHOT	Acute Myocardial Infarction With Hyperoxemic Therapy
AN	Area of Necrosis
AO Therapy	Aqueous Oxygen Therapy
AOCS	AO Cartridge Subsystem
apO ₂	Arterial Blood Partial Oxygen Pressure (solubilized equivalent)
APSAC	Anisoylated Purified Streptokinase Activator Complex
AR	Area at Risk
ARC	Academic Research Consortium
ASA	Acetyl Salicylic Acid
AST	Asparatate Aminotransferase
BMC	Blood Mixing Chamber
BMI	Body Mass Index
BMS	Bare Metal Stent
BP	Blood Pressure
BPM	Beats Per Minute
BUN	Blood Urea Nitrogen
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CADILLAC	Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications
CARE	Cholesterol and Recurrent Events

CBC	Complete Blood Count
CCS	Canadian Cardiovascular Society
CCL	Cardiac Catheterization Laboratory
CCU	Cardiac Care Unit
CDP	Clinical Discovery Platform
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CHF	Congestive Heart Failure
CI	Clinically Indicated
CK	Creatine Kinase
CK-MB	Creatine Kinase Myocardial-Band Isoenzyme
cm	Centimeter
CORE	Collaborative Organization for RheothRx Evaluation
COURAGE	Clinical Outcomes Using Revascularization and Aggressive Drug Evaluation
CPR	Cardiopulmonary Resuscitation
CRA	Clinical Research Associate
CRF	Cardiology Research Foundation
CRF	Case Report Form
CRO	Clinical Research Organization
CSS	Coronary Stent System
CTFC	Corrected TIMI Frame Count
CTO	Chronic Total Occlusion
CVA	Cerebral Vascular Accident
D2B	Door To Balloon
DBP	Diastolic Blood Pressure
DCF	Data Clarification Form
DES	Drug Eluting Stent
dL	Deciliter
DS	Diameter Stenosis
DSMB	Data Safety Monitoring Board
eECG	Electronic Electrocardiographic
ECG	Electrocardiogram
EECSS	Everolimus Eluting Coronary Stent System

EF	Ejection Fraction
EMERALD	Enhanced Myocardial Efficacy and Removal by Aspiration of Liberated Debris
ER	Emergency Room
EtO	Ethylene Oxide
FDA	Food and Drug Administration
FU	Follow Up
g	grams
GCP	Good Clinical Practice
GERD	Gastro-Esophageal Reflux Disorder
GGPT	Gamma Glutamyl Transferase
GI	Gastrointestinal
GIK	Glucose Insulin Potassium
GP	Glycoprotein
GU	Gastric Ulcer
Hct	Hematocrit
HDL	High Density Lipoprotein
Hgb	Hemoglobin
HORIZONS	Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction Study
IABP	Intra-Aortic Balloon Pump
IC	Intra Coronary
ICD	Implantable Cardiac Defibrillator
IDE	Investigational Device Exemption
IFU	Instructions For Use
IMV	Interim Monitoring Visit
IQR	Interquartile Range
IRA	Infarct Related Artery
IRB	Institutional Review Board
ITT	Intent To Treat
IV	Intravenous
IVUS	Intravascular Ultrasound
LAD	Left Anterior Descending Coronary Artery
LBBB	Left Bundle Branch Block

LCX	Left Circumflex Coronary Artery
LDH	Lactate Dehydrogenase
LDL	Low Density Lipoprotein
LL	Late Loss
LMWH	Low Molecular Weight Heparin
LV	Left Ventricle
LVEF	Left Ventricular Ejection Fraction
MACE	Major Adverse Cardiac Event
MeDRA	Medical Dictionary fro Regulatory Activities
MDR	Medical Device Reporting
mg	Milligram
MI	Myocardial Infarction
MLD	Minimum Lumen Diameter
mm	Millimeter
mmHg	Millimeter of Mercury
MPO	Myeloperoxidase
MRI	Magnetic Resonance Imaging
NEJM	New England Journal of Medicine
NR-MI-4	National Registry of Myocardial Infarction
NTG	Nitroglycerine
OD	Outer Diameter
OUS	Outside the United States
OYSTER-AMI	Oxygen in ST-Elevation Reperfused Acute Myocardial Infarction
PCI	Percutaneous Coronary Intervention
PES	Paclitaxel-Eluting Stent
PI	Principal Investigator
PO	Per Os
pO ₂	Partial Oxygen Pressure (or solubilized equivalent)
PP	Per Protocol
PTCA	Percutaneous Transluminal Coronary Angioplasty
QC	Quality Control
QCA	Quantitative Coronary Angiography
QD	Every Day

RBC	Red Blood Cells
RCA	Right Coronary Artery
RCT	Randomized Clinical Trial
RR	Relative Risk
r-TPA	Recombinant Tissue Plasminogen Activator
RVD	Reference Vessel Diameter
RWMSI	Regional Wall Motion Score Index
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SD	Standard Deviation
SE	Standard Error
SES	Sirolimus-Eluting Stent
SPECT	Single Photon Emission Computer Tomography
SSO ₂	Supersaturated Oxygenation
STEMI	ST-Elevation Myocardial Infarction
STP	Standard Temperature and Pressure (25°C, 1 atmosphere)
TCT	Transcatheter Therapeutics Meeting
TEE	Trans Esophageal Echocardiogram
TIA	Transient Ischemic Neurological Attack
TIMI	Thrombolysis in Myocardial Infarction
TLR	Target Lesion Revascularization
TNK	Tenecteplase
TTC	Triphenyl Tetrazolium Chloride
TVF	Target Vessel Failure
TVR	Target Vessel Revascularization
µg	Microgram
UK	United Kingdom
URL	Upper Reference Limit
USA	United States of America
VSD	Ventricular-Septal Defect
WBC	White Blood Cells
WD	Withdrew
WHO	World Health Organization

17.3 Appendix III: Trial Flow

Patient considered for DownStream PAS?

Yes



Informed Consent obtained?

Yes



Anterior < 6 hr. STEMI with successful PCI/Stent procedure?

Yes



Patient enrolled into PAS?

Yes



Patient administered SSO₂ Therapy?

Yes



Telephone contact or office visit at 30 days (+/- 7 days)

Yes



Telephone contact or office visit at 180 days (+/- 14 days)

Yes



Telephone contact or office visit (1 year +/- 30 days)

Yes

17.4 Appendix IV: Schedule of Events

Informed Consent	√									
Demographic: age, gender, race	√ ¹									
Medical Hx and Risk Factors: cardiac, diabetes, HTN, CABG, PCI, CAD, dyslipidemia, renal insufficiency, anemia, tobacco, stroke	√ ¹									
Physical Measurements: wt., ht., HR/BP	√ ¹			√	√	√	√			
Laboratory Assessment: CBC, lipid profile, creatinine	√ ¹						√			
Cardiac Enzymes: CK, CK-MB , and/or Troponin	√ ¹		√							
ECG	√ ¹		√							
Eligibility Criteria Met	√ ¹									
Antiplatelet loading dose		√								
Stenting used and lesion characteristics		√								
Coronary angiogram with TIMI flow assessment	√		√							
pO ₂ & ACT				√	√	√				
Study F/U Instructions								√	√	√
F/U Survey/ Questionnaire								√	√	√
Antiplatelet therapy, chronic concomitant medications	√ ¹	√	√				√	√	√	√
Adverse Events	√	√	√	√	√	√	√	√	√	√

¹Baseline or post-procedure if not collected at baseline.

17.5 Appendix V: DownStream AO System Operators Manual
(to be provided separately)

17.6 Appendix VI: Instructions For Use
(to be provided separately)